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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/811,346	03/16/2001	David Nanus	ARG-912-C1	1693

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KLAUBER & JACKSON
411 HACKENSACK AVENUE
HACKENSACK, NJ 07601

EXAMINER	
CANELLA, KAREN A	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 12/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/811,346	NANUS, DAVID	
	Examiner	Art Unit	
	Karen A Canella	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 8-34* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6,8-17,19-26,28-31,35-45 and 47* is/are rejected.

7)☒ Claim(s) *18,27,32-34,46 and 48* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *8/16/04+6/16/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 9 has been amended. Claim 7 has been canceled. Claims 35-48 have been added. Claims 1-6 and 8-34 are pending and under consideration.

2. The text of sections of Title 35, U.S. Code not found in this action can be found in a previous action.

3. The rejection of claims 1-6, 8-17, 19-25, 28-31 under 35 U.S.C. 103(a) as being unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134, pp. 99-104, reference of the IDS filed June 16, 2003) in view of Parthasarathy et al (Cancer Letters, 1998, Vol. 134, pp. 121-128, cited in a previous Office action) and Regazzi et al (Clinical Pharmokinetics, 1997, Vol. 32, pp. 382-402) is maintained for reasons of record. New claims 35-45 and 47 are also rejected for the same reasons of record..

Claim 1 is drawn to a method of inhibiting the growth of cancer cells comprising exposing cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a retinoid wherein said retinoid is associated with lipid carrier particles. Claim 2 embodies the method of claim 1 wherein the retinoid is retinoic acid. Claim 3 embodies the method of claim 2 wherein the retinoic acid is all-trans retinoic acid. Claim 17 embodies the method of claim 3 wherein the amount of all-trans retinoic acid is about 15-300 mg/m2. Claim 4 embodies the method of claim 1 wherein the lipid carrier particles comprising all-trans retinoic acid, lipid and a triglyceride, wherein a molar ratio of retinoid to lipid is at least about 15:85, the triglyceride is at least 15% by weight of the composition, wherein said composition is stable in an aqueous environment. Claim 29 embodies the method of claim 4 wherein the cancer is a renal cancer. Claim 5 embodies the method of claim 1 comprising administering said retinoid composition by intravenous infusion. Claim 6 embodies the method of claim 1 wherein the composition comprising at least one interferon and a retinoid is administered at a frequency from daily to about 3 out of 7 days a week.

Claim 8 is drawn to a method of inhibiting the growth of cancer cells comprising co-timely exposing cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a therapeutically effective amount of a retinoid, wherein

said retinoid is associated with lipid carrier particles. Claim 35 embodies the method of claim 8 wherein said retinoid is ATRA. Claim 36 embodies the method of claim 8 wherein the lipid carrier particles comprising all-trans retinoic acid, lipid and a triglyceride, wherein a molar ratio of retinoid to lipid is at least about 15:85, the triglyceride is at least 15% by weight of the composition, wherein said composition is stable in an aqueous environment. Claim 10 and 11 embody the methods of claims 1 and 8, respectively, wherein the cancer is selected from the group consisting of renal cancer, breast cancer, head cancer and neck cancer. Claims 30 and 31 embody the methods of claims 10 and 11, respectively, wherein the cancer is a renal cancer. Claims 12 and 13 embody the methods of claims 1 and 8 respectively, wherein the cancerous cells are exposed in vivo. Claims 14 and 19 embody the methods of claims 1 and 8, respectively, wherein the interferon is selected from the group consisting of alpha, beta and gamma interferon. Claims 15 and 20 specify that the interferon of claims 14 and 19 is alpha interferon. Claims 16 and 21 embody the methods of claims 15 and 20, respectively, wherein the alpha-interferon is administered in an amount of about 1 to about 25 million IU.

Claim 9 is drawn to a therapeutic treatment kit for the treatment of cancer comprising interferon, all-trans retinoic acid associated with lipid carrier particles and instructional materials for the combined use of said all-trans retinoic acid associated with lipid carrier particles and interferon. Claim 37 embodies the kit of claim 9 wherein said interferon comprises alpha IFN. Claim 38 embodies the kit of claim 9 wherein the lipid carrier particles comprising all-trans retinoic acid, lipid and a triglyceride, wherein a molar ratio of retinoid to lipid is at least about 15:85, the triglyceride is at least 15% by weight of the composition, wherein said composition is stable in an aqueous environment. Claim 39 is drawn to a therapeutic treatment kit comprising interferon, a retinoid associated with lipid carrier particles and instructional materials for the combined use of said retinoid associated with lipid carrier particles and interferon.

Claim 22 is drawn to a method of inhibiting the growth of cancer cells, wherein the cancer cells are selected from the group consisting of renal, head, neck and breast cancer cells, comprising exposing said cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a retinoid, wherein the retinoid is all-trans retinoic acid and is associated with lipid carrier particles. Claim 23 embodies the method of claim 22 wherein the interferon is selected from the group consisting of alpha, beta and gamma interferon.

Claim 24 specifies that the interferon of claim 23 is alpha interferon. Claim 25 embodies the method of claim 24, wherein the alpha interferon is administer in an amount of about 1 to about 25 million IU. Claim 26 embodies the method of claim 22 wherein the amount of all-trans retinoic acid is about 15-300 mg/m2. Claim 40 embodies the method of claim 22 wherein the lipid carrier particles comprising all-trans retinoic acid, lipid and a triglyceride, wherein a molar ratio of retinoid to lipid is at least about 15:85, the triglyceride is at least 15% by weight of the composition, wherein said composition is stable in an aqueous environment. Claim 41 embodies the method of claim 22 wherein the cancer cells are renal cancer cells.

Claim 28 is drawn to a method of inhibiting the growth of cancer cells, wherein the cancer cells are selected from the group consisting of renal, head, neck and breast cancer cells comprising exposing said cancerous cells to a therapeutically effective amount of a composition which comprises at least one interferon and a retinoid, wherein the retinoid is all-trans retinoic acid and is associated with lipid carrier particle and the at least one interferon is alpha interferon. Claim 43 embodies the method of claim 28 wherein the cancer cells are renal cancer cells. Claim 44 embodies the method of claim 28 wherein the cancerous cells are exposed in vivo. Claim 45 embodies the method of claim 28 wherein the alpha interferon is administered in an amount of about 1 to about 25 million IU. Claim 47 embodies the method of claim 28 wherein the amount of ATRA is about 15-300 mg/m2.

Bonhomme-Faivre et al teach the treatment of patients with advanced renal cancer comprising the administration of ATRA at 100 mg/m2/day concomitantly with IFN-alpha (9-18 million IU/m2), three days a week, thus fulfilling the specific embodiment of claim 6 drawn to daily to about 3 out of 7 days per week, the specific embodiments of claims 16, 21, 25 and 45 drawn to the administration of alpha interferon in an amount of about 1 to about 25 million IU, and the specific embodiments of claims 17, 26 and 47 drawn to the administration of all-trans retinoic acid in an amount of about 15-300 mg/m2. Bonhomme-Faivre et al teach that ATRA binds to serum albumin in plasma where it is rapidly taken up by the liver and metabolized (page 99, second column, last paragraph). Bonhomme-Faivre et al teach that the combination of ATRA and IFN possess an enhanced anti-proliferative effect on some renal cancer cell lines (page 100, first column, lines 27-31). Bonhomme-Faivre et al teach that the plasma concentrations of ATRA were relatively low in the patients that were studied (page 102, second

column, lines 6-7 under the heading "Discussion"). Bonhomme-Faivre et al teach that IFN increased peak plasma levels of ATRA and reduced the clearance rate of ATRA (page 102, first column, lines 17-20) by means of depressing the hepatic cytochrome P450 drug metabolizing system and enhances in vivo ATRA effects (page 100, first column, lines 24-27 and page 103, first column, lines 14-19). Bonhomme-Faivre et al teach that administration of ATRA on an intermittent basis allows for the circumvention of the elevated plasma clearance rate of ATRA, but may be associated with lower clinical efficacy (page 103, first column, lines 20-26). Bonhomme-Faivre et al teach co-administration of IFN and ATRA should be expected to increase peak plasma levels of ATRA and decrease clearance of ATRA (page 103, first column, lines 27-29). Bonhomme-Faivre et al do not teach the intravenous administration of ATRA associated with lipid carrier particles.

Parthasarathy et al teach that encapsulation of ATRA in lipid vesicles reduced in vitro toxicity and retains the full biological activity of the ATRA. Parthasarathy et al teach that encapsulation of ATRA in liposomes protects the drug from catabolic enzymes and decreases exposure of normal tissues to retinoid (page 125, second column, lines 19-26) and thus results in the higher exposure of target cells to the active form of ATRA for longer periods (page 126, second column, last sentence of the last full paragraph). Parthasarathy et al teach that accumulation of liposomes in reticuloendothelial organs, such as the liver and spleen can be circumvented by the use of cationic liposomes, (such as the liposomes formulated by diphosphatidyl palmitoylcholine and stearylamine in a 9:1 ratio, which when converted to a molar ratio corresponds to the limitations of claims 4, 36, 38, 40 and 42) rather than anionic liposomes (page 125, second column, lines 17-19 of the last paragraph). Parthasarathy et al teach that orally administered ATRA not encapsulated in a liposome accumulates predominately in hepatocytes (page 125-126, bridging sentence and page 126, second column, lines 1-5 of the first full paragraph) and that only 20-25% of lipsosomal ATRA administered intravenously accumulates in the liver and Kupffer cells.

Regazzi et al teach a new formulation of all-trans retinoic acid (tretinoin) developed for intravenous administration to provide pharmacological advantages over the oral formulation of tretinoin. Regazzi et al teach that animal treated long term with intravenous liposomal tretinoin metabolized retinoic acid to a lesser extent than animals treated with free tretinoin. Regazzi et al

teach that lipid formulation bypasses the clearance mechanism which evolves in the liver of patients treated with oral tretinoin. Regazzi et al conclude that the liposomal formulation should not result in the same relapse rate which has been demonstrated in clinical trials with oral tretinoin administration, and should decrease the direct exposure of he drug during circulation to concentrations below the orally administered toxic dose resulting in less serve side effects (page 398-399, bridging paragraph).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to administer the liposomal encapsulated ATRA of Parthasarathy et al in place of free ATRA in the method taught by Bonhomme-Faivre et al . It would also have been prima facie obvious to package both liposomal encapsulated ATRA and interferon alpha in a kit for the convenience of administration to patients having renal cell carcinoma. One of skill in the art would have been motivated to do so by the teachings of both Parthasarathy et al and Regazzi et al on the decreased toxicity, and decreased metabolic clearance associated with liposomal ATRA versus free ATRA. One of skill in the art would be motivated to reduce hepatic accumulation and clearance in order to provide more of the administered dose to the target tissue.

4. Applicant argues in the middle of page 9 that because Bonhomme-Faivre refer to the paper as "preliminary" this somehow discredits the facts reported therein. This has been considered but not found persuasive. Page 102, second column, it is stated that "These preliminary results showed no relationship between the maximum plasma concentration and ATRA and the response to treatment". The specific qualification of "preliminary" is in obvious reference to a full fledged clinical trial. However, as of the filing date of the instant specification, one of skill in the art after reading of Bonhomme-Faivre et al would not find reasons to doubt the validity of the result. Further, Bonhomme-Faivre et al provide the motivation to optimize clinical efficacy comprising determining an interferon dosing schedule which would allow plasma levels of ATRA to be maintained or increased during chronic ATRA treatment. Applicant argues that one of skill in the art would certainly not view this reference as definitive because of the "preliminary study". This has been considered but not found persuasive because the reference need not be definitive, it need only have a reasonable expectation of

success. M.P.E.P. (2143.02): The prior art can be modified or combined to reject claims as prima facie obvious as long as there is a reasonable expectation of success.

Applicant argues that the results of Bonhomme-Faivre et al appear to conflict with that of Smith. This has been considered but not found persuasive. Bonhomme-Faivre et al state that the IFN dosage used by Smith was 3 million IU twice a week and therefore the patients in Smiths study were exposed to less IFN. One of skill in the art would know that a direct comparison cannot be made between Smith and Bonhomme-Faivre because of the effect of IFN on the ATRA level in the patient serum. A lower administered dose of IFN would not be expected to affect the ATRA levels to the same extent as that which was observed by Bonhomme-Faivre and any potential additive or synergistic effect would not be realized.

Applicant argues on the top o page 10 that Bonhomme-Faivre lacks teachings or suggestion of intravenous administration of ATRA with IFN. Applicant is reminded that if Bonhomme-Faivre did indeed teach those limitations, the rejection would have been under 102 rather than 103.

Applicant argues on page 11 that Parthasarathy et al teaches away from the present invention because it is directed toward the administration of L-ATRA which is recognized in the art as an alternative solution to the combination or oral retinoid/IFN therapy. This has been considered but not found persuasive. No facts have been presented to substantiate the allegation that the art recognizes that L-ATRA is an alternative solution to combination retinoid/IFN therapy. Cancer therapy is continually in flux. There are no absolute standards for the treatment of cancers because all known treatments are less than optimally efficacious in that not all of the patients respond to any given treatment regiments, and not all of the patients exhibit disease free survival after treatment. One of skill in the art would be highly motivated to modify any existing treatment in order to increase patient response, prolong patient survival and prolong patient disease free survival. Further the teachings of M.P.E.P. (2123) regarding the disclosure of non-preferred embodiments "Disclosed examples and preferred embodiments do not constitute a teaching away from a broader disclosure or nonpreferred embodiments. In re Susi, 440 F.2d 442, 169 USPQ 423 (CCPA 1971)." is directly applicable to the type of reasoning set forth by applicant. By stating that it is recognized in the art that patients are treated by retinoid combined with INF or treated with liposomal tensioning, applicant is stating that the "preferred

embodiments" recognized by the art are combined treatment with retinoid and IFN are "preferred embodiment" and single agent "liposomal tretinoin" is a separate preferred embodiment. There is nothing in the patent law that dictates that a commonly used combination treatment which gives some limited success in the treatment of cancer cannot be the basis for a new combination treatment wherein one of the drugs is modified in some way to give a greater expectation of greater success in the amelioration of the cancer

Applicant argues on the bottom of page 11 that Regazzi et al teaches away from the instant invention with the statement that liposomal tretinoin was impractical for extended therapy because of the need for intravenous administration, and the instant claim 5 requires intravenous infusion of the retinoid. This has been considered but not found persuasive. Regazzi et al is relied upon for teachings regarding the pharmokinetics of liposomal tretinoin, not for the duration of the administration. Further Regazzi et al is clearly speculating when stating that the liposomal form of tretinoin is "probably impractical". This is only in reference to cost and convenience of the treatment. One of skill in the art would know that a patient suffering from cancer would want a treatment which would decrease the degree of cancer in said patient and preferably allow said patient a prolonged survival without consideration as to the cost or the convenience of the treatment. It is noteworthy that the instant specification provides no suggestions for how to decrease the cost or the inconvenience of intravenous administration of liposomal retinoid in combination with IFN. Further the successful management of long-term intravenous therapy in cancer patients was reported decades ago to have "an acceptably low complication rate in a high-risk patient population" (the abstract of Bottino et al, Cancer, 1979, Vol. 5, pp. 1937-1943), thus corroborating the examiners assertion that the high risk population of cancer patients would place a different value on long term intravenous therapy, than patients in other groups associated with lower risk of disease associated death.

Applicant again argues on page 12 that Regazzi et al offers liposomal tretinoin as alternative to tretinoin and IFN alpha and that this somehow teaches away from using it in the instant rejection. As stated above, no facts have been presented to substantiate the allegation that the art recognizes that L-ATRA is an alternative solution to combination retinoid/IFN therapy. Cancer therapy is in continually in flux. There are no absolute standards for the treatment of cancers because all known treatments are less than optimally efficacious in that not all of the

patients respond to any given treatment regiments, and not all of the patients exhibit disease free survival after treatment. One of skill in the art would be highly motivated to modify any existing treatment in order to increase patient response, prolong patient survival and prolong patient disease free survival.

Applicant argues in the middle of page 12 that the examiner is interpreting the prior art references in light of the invention and concludes that improper use of hindsight has rendered the obviousness rejection invalid. The M.P.E.P. (2145) states that

5. Applicants may argue that the examiner's conclusion of obviousness is based on improper hindsight reasoning. However, "[a]ny judgement on obviousness is in a sense necessarily a reconstruction based on hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill in the art at the time the claimed invention was made and does not include knowledge gleaned only from applicant's disclosure, such a reconstruction is proper." In re McLaughlin 443 F.2d 1392, 1395, 170 USPQ 209, 212 (CCPA 1971). >Applicants may also argue that the combination of two or more references is "hindsight" because "express" motivation to combine the references is lacking. However, there is no requirement that an "express, written motivation to combine must appear in prior art references before a finding of obviousness." See Ruiz v. A.B. Chance Co., 357 F.3d 1270, 1276, 69 USPQ2d 1686, 1690 (Fed. Cir. 2004). For example, motivation to combine prior art references may exist in the nature of the problem to be solved (Ruiz at 1276, 69 USPQ2d at 1690) or the knowledge of one of ordinary skill in the art (National Steel Car v. Canadian Pacific Railway Ltd., 357 F.3d 1319, 1338, 69 USPQ2d 1641, 1656 (Fed. Cir. 2004)).

6. The rejection of claims 1-6, 8-17, 19-25, 28-31 under 35 U.S.C. 103(a) as being unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134, pp. 99-104) and Parthasarathy et al (Cancer Letters, 1998, Vol. 134, pp. 121-128) and Regazzi et al (Clinical Pharmacokinetics, 1997, Vol. 32, pp. 382-402) as applied to claims 1-17, 19-25, 28-31, above, and further in view of Lippman et al (International Journal of Cancer, 1997, Vol. 70, pp. 481-483, reference of the IDS filed June 16, 2003) and Parthasarathy et al (Cancer

Chemother Pharmacol, 1994, vol. 34, pp. 527-534) is maintained for reasons of record. New Claims 35-45 and 47 are also included in this rejection..

Claims 10, 11, 22 and 28 recite the specific embodiments of head and neck cancer. The combination of Bonhomme-Faivre et al, Parthasarathy et al (1998) and Ragazzi et al render obvious a method of treating renal cell cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha for the reasons set forth above. The combination does not render obvious a method of treating head and neck cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha.

Lippman et al teach a method for treating squamous cell carcinoma comprising the administration of 13-cis-retinoic acid and IFN (interferon alpha). Lippman et al teach that the largest disease group in the phase II clinical study were head/neck and skin cancers, and that a 50% response rate was attained in these two major disease groups (page 481, first column, lines 23-28).

Parthasarathy et al (1994) teach that liposomes formulated with dipalmitoylphsohatidycholine and stearylamine showed the optimal combination of low toxicity to red blood cells and effective delivery to target cells (page 530, second column, lines 6-11). Parthasarathy et al teach that said liposomes effective delivered 5600 pmol ATRA/mg protein in MDA 886Ln cells. (page 531, second column, lines 9-14). MDA 886Ln cells were derived from a metastatic lesion of squamous cell carcinoma of the larynx (page 528, first sentence under the heading of "Cell culture"). Parthasarathy et al teach that encapsulating retinoid may provide a means for delivering said retinoid without the resulting toxicity, sequester the drug as particles at tumor locations, protect the drug from rapid metabolism, amplify its therapeutic effect, and improve the solubility of lipophilic drugs such as retinoid (page 528, first column, lines 3-9)

It would have been prima facie obvious to one of skill in the art at the time the invention was made to substitute liposomal ATRA for the free 13-cis-retinoic acid in the method of treating head and neck cancers as taught by Lippman et al. One of skill in the art would be motivated to do so by the teachings of Parthasarathy et al (1994) on the high level of ATRA delivered to SCC cells by means of liposomal encapsulated proteins, and on the advantages associated with the use of liposomal retinoid which include decreased toxicity, decreased hepatic clearance and the sequestering of liposomal particles at the tumor site. One of skill in the art

would be motivated to increase the local concentration of ATRA at the tumor site and decrease hepatic uptake and clearance in order to provide a higher dose of ATRA to the tumor cells without increasing the administered dose, and thus decreasing the side effects associated with ATRA administration.

7. Applicant argues near the bottom of page 13 that neither the Lippman et al reference or the Parthasarathy et al (1994) reference remedies the deficiencies of Bonhomme-Faivre or Parthasarathy et al (1998) or Regazzi et al. This has been considered ed but not found persuasive. The combination of Bonhomme-Faivre and Parthasarathy et al (1998) and Regazzi et al render obvious the instant claims 1-6, 8-17, 19-25, 28-31, 35-45 and 47 for the reasons set forth and maintained above. The anticipatory nature of the references in isolation is not relevant to the rejection based on the combination of references.

8. The rejection of claims 1-6, 8-17, 19-25, 28-31 under 35 U.S.C. 103(a) as being unpatentable over Bonhomme-Faivre (International Journal of Pharmaceutics, 1996, Vol. 134, pp. 99-104) and Parthasarathy et al (Cancer Letters, 1998, Vol. 134, pp. 121-128) and Regazzi et al (Clinical Pharmacokinetics, 1997, Vol. 32, pp. 382-402) as applied to claims 1-6, 8-17, 19-25, 28-31 above, and further in view of Marth et al (Journal of the National Cancer Institute, 1986, vol. 77, pp. 1197-1202, reference of the IDS filed June 16, 2003) and Parthasarathy et al (Cancer Chemother Pharmacol, 1994, vol. 34, pp. 527-534) is maintained for reasons of record and also applied to new claims 35-45 and 47.

Claims 10, 11, 22 and 28 recite the specific embodiments of breast cancer. The combination of Bonhomme-Faivre et al, Parthasarathy et al (1998) and Ragazzi et al render obvious a method of treating renal cell cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha for the reasons set forth above. The combination does not render obvious a method of treating breast cancer comprising the concurrent administration of liposome encapsulated ATRA and IFN-alpha.

Parthasarathy et al teach that encapsulating retinoid may provide a means for delivering said retinoid without the resulting toxicity, sequester the drug as particles at tumor locations,

protect the drug from rapid metabolism, amplify its therapeutic effect, and improve the solubility of lipophilic drugs such as retinoid (page 528, first column, lines 3-9).

Marth et al teach that IFN-alpha and all-trans retinoic acid exerted synergistic antiproliferative effects on culture breast cancer cells (Figure 1).

It would have been prima facie obvious to one of skill in the art at the time the invention was made to treat breast cancer with liposomal ATRA and IFN-alpha. One of skill in the art would be motivated to do so by the teachings of Parthasarathy et al (1994) on the advantages associated with the use of liposomal retinoid which include decreased toxicity, decreased hepatic clearance and the sequestering of liposomal particles at the tumor site. One of skill in the art would be motivated to increase the local concentration of ATRA at the tumor site and decrease hepatic uptake and clearance in order to provide a higher dose of ATRA to the tumor cells without increasing the administered dose, and thus decreasing the side effects associated with ATRA administration. One of skill in the art would be motivated to combine ATRA and IFN-alpha in a treatment of breast cancer because the two agent exert a synergistic effect on cultured breast cancer cells.

9. Applicant argues near the bottom of page 14 that neither Marth et al nor the Parthasarathy (1994) reference , or a combination thereof remedy the defects of deficiencies of Bonhomme-Faivre or Parthasarathy et al (1998) or Regazzi et al. This has been considered ed but not found persuasive. The combination of Bonhomme-Faivre and Parthasarathy et al (1998) and Regazzi et al render obvious the instant claims 1-6, 8-17, 19-25, 28-31, 35-45 and 47 for the reasons set forth and maintained above. The anticipatory nature of the references in isolation is not relevant to the rejection based on the combination of references.

10. Claims 18, 27, 32-34, 46 and 48 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

11. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10 a.m. to 9 p.m. M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571)272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Karen A. Canella, Ph.D
11/29/30